Genetics for the Internist - I

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Why do we have to know this?

- Board examination
- Residency examination
- Wardsmanship
- Intellectual stimulation
- Patient Care
- Your friends will ask you

Resources I have chosen

- Mayo Internal Medicine Board Review 1996-1997
- MKSAP 10
- Current literature
- Computer databases - OMIM, NIH Genetics

Overview of Genetic Concepts

- Basic human genetic principles
  - context of everyday clinical practice
- relevance of human genome project
  - how genes behave in families and individuals
- major forms of human inheritance
- importance of clinical laboratory
  - ID of at risk individuals
- clinical laboratory techniques available
- management of hereditary disorders

Introduction

- Chromosome Abnormalities
- Patterns of Inheritance
  - Mendelian
  - Non-Mendelian
    - Mitochondrial mutations
    - Multifactorial inheritance
- Presymptomatic diagnosis
- Prenatal diagnosis
- Molecular strategies

Inheritance

- Chromosomal
  - numerical, structural, microdeletions
- Single gene - CF, Sickle cell
- Multifactorial
  - CHD, pyloric stenosis, Cleft lip/palate, NTDs
- Triplet nucleotide repeats
- Mitochondrial inheritance

Inheritance

- UPD - Uniparental disomy
- Imprinting - Prader willi, Angleman - 15 q 21
- Trinucleotide repeat sequences
  - Fragile X, Myotonic dystrophy, Huntington Disease, SBMA
- Mitochondrial inheritance
  - MELAS, LHON Leber’s hereditary optic neuopathy

Hints that Genetic Cause is likely

- Atypical age of onset - Angina before 50
- Episodic occurrences - Acute intermittent porphyria, periodic paralysis, recurrent syncope
- Multiple occurrences - Bilateral tumors, multiple primary tumors, multiple cafe au lait spots (NF)
- Seemingly unrelated conditions - presenting symptom plus MR, infertility or cong malf

Some examples of Genetic Disorders in IM

- Familial Long QT syndrome
- BRCA1 - breast/ovarian CA susceptibility
- Neuofibromatosis 1 and 2
- Alzheimer’s disease - apolipoprotein E locus
- Gaucher’s disease
- Osler-Weber-Rendu syndrome
- Hypertension

Will changes in Medicine affect Genetics?

- Re-orientation of health care
- Increased emphasis on preventive health
  - inherited risks
- standardized reimbursement
  - encourage more extensive clinical genetics services
- identification of heritable susceptibilities to common diseases

Biotechnology Industry

- marketing of clinical laboratory tests
- pharmaceuticals
- focusing attention on genetics
- health-care administrators, politicians, insurers

Social Forces

- improved genetic education in public schools
- emphasis on preventive medicine
- increased expectation of health

Diagnosis of Genetic Disorders

- Cytogenetic analysis
  - karyotype
  - clinical indications for cytogenetic analysis
- Cancers arising from multiple genetic alterations
- Metabolic and Biochemical testing
- Linkage analysis of genetic disorders

Management of Genetic Disorders

- Genetic Counseling
- Avoidance strategies, Dietary supplements, and drug therapies
- Organ transplantation and surgical interventions
- Genetic therapy

Chromosome Abnormalities

- occur in 1 in 800 live births
- risk factors for autosomal aneuploidy:
  - maternal age > 35 years
  - having had an affected child

Down syndrome

- most common autosomal aneuploidy syndrome in term infants
- most serious consequence is mild to moderate mental retardation
- most frequent heart defect is VSD or Atrioventricular canal defect
- Males with DS are usually sterile, but females are fertile
- Most persons with DS have trisomy 21

Down syndrome

- Full trisomy - 94%
- 21 trisomy/normal mosaicism - 2.4%
- Translocation cases - 3.3%
  - about equal occurrence of D/G and G/G translocation

Down syndrome

- 1 in 660 newborns overall
- increased in women by age - 1 in 385 at 35
- Congenital heart defects - primary cause of early mortality
  - with CHD survival is 76% at 1 year
  - age 5, 61%; age 10, 57%
- Increased incidence of leukemias
- mean IQ - 24 in older patients

Sex Chromosome Aneuploidy Syndromes

- 47,XXY (Klinefelter): small testes, infertility, tall eunuchoid body habitus
- 45,X (Turner): short stature, lack of secondary sex characteristics, usually mentally normal, 30% risk of congenital heart defect (coarc of aorta) and bicuspid aortic valve
  - webbed neck, increased number of pigmented nevi, short 4th or 5th metatarsals/carpals

Other Chromosome Abnormalities

- 34% of chrom abnormalities involve structural changes
  - deletions, duplication, inversions, translocations
- Balanced translocations - usually phenotypically normal
  - may be at increased risk for miscarriages
  - children may have birth defects
- Parents of all children with structural chromosome abnormality should have chromosome analysis

Fragile X-Linked Mental Retardation

- fragile site on long arm of X - band q27
- males with FraX: may be physically normal or have long, thin face, prominent jaw, large ears, enlarged testes, mild to profound MR
- carrier females: phenotypically normal or mildly retarded and dysmorphic
- Mutation - trinucleotide repeat (CGG) expanded into hundreds
  - direct DNA analysis most accurate

Patterns of Inheritance

- Autosomal dominant
- Autosomal recessive
- X - linked dominant
- X - linked recessive

Autosomal Dominant

- Ehlers-Danlos
- Hypertrophic cardiomyopathy
- Marfan syndrome
- Myotonic Dystrophy
- Nurofibromatosis - type 1 and 2
- Osteogenesis imperfecta
- Tuberous sclerosis
- Von Hippel-Lindau Disease

EDS type I - AD condition

- Features: velvety textured, hyperextensible, fragile skin
- Joints are hyperextensible and prone to dislocation
- Associated conditions: pes planus, scoliosis, degenerative arthritis, visceral diverticulosis, spontaneous pneumothorax
- mitral valve prolapse in 50%
- vascular rupture uncommon

EDS type II - mitis - AD

- similar to I but milder
- AD inheritance
- mitral valve prolapse common

EDS type III - benign familial hypermobility

- joint dislocations are common
- skin hyperextensibility and scarring are minimal or absent
- wide range of expression both within and between families
- people with this disorder merge with the normal pop

EDS type IV - vascular type

- genetically heterogeneous - AD, AR
- **most severe form** / MVP common
- **deficiency of type III collagen** synthesis or secretion in skin, aorta, uterus and intestine
- **rupture** of large arteries, colon, gravid uterus
- Angiography or other invasive procedures may precipitate vascular or organ rupture
- Occasional: spontaneous pneumothorax, severe periodontal disease

EDS type V

- X - linked recessive
- associated with lysyl oxidase deficiency
- skin hyperextensibility severe
- joint hypermobility - mild/moderate
- mitral and tricuspid valve prolapse or insuffiency may be present

EDS type VI - Ocular type

- blindness from retinal detachment is complication
- AD or AR - AR form sometimes seen with deficiency of procollagen lysyl hydroxylase
- Severe scoliosis, joint dislocations, aortic rupture, GI hemorrhage can occur

EDS type VII

- arthrochalasis multiplex congenita
- extreme joint laxity and dislocations
- AR form - defective conversion of procollagen to collagen
- AD form - more common - structural abnormalities of half their alpha-2 chains of type I collagen which interfere with the conversion of procollagen to collagen

Hypertrophic Cardiomyopathy

- AD, penetrance = 75% - 100%
- Investigate all first degree relatives
  - EKG and ECHO
- Children born to affected parent must be considered at risk and should be evaluated

Hypertrophic Cardiomyopathy

- Course of disease is variable
- Age of onset cannot be predicted
- 50% of families with HC have defect in B-cardiac myosin heavy-chain gene on chromosome 14
- Genetic heterogeneity - other families have not shown this linkage to Chr 14

Marfan Syndrome

- relatively common disorder of connective tissue
- incidence = 1 in 20,000
- AD with extremely variable expression
- 20% are new mutations
- Non-penetrance has never been documented

Marfan Syndrome

- involves the musculoskeletal, cardiovascular and ocular systems
- skeletal: tall stature, low upper: lower segment ratio, scoliosis or kyphosis, pectus deformities
- ocular: subluxation of lenses, myopia and retinal detachment

Dislocation of Lenses - Differential DX

- Marfan - occurs in 50-80% of patients
  - lens frequently displaced upward
- Homocystinuria
- Weill-Marchesani syndrome
- ALL patients with Marfan S must have
  - complete ophthalmologic exam -
  - slit-lamp exam permits early detection of complications such as retinal detachment and glaucoma

Marfan Syndrome

- life expectancy shortened by CV disease
- most common CV manifestations are mitral valve prolapse and dilation of the ascending aorta
- more than 80 of patients have abnormalities on echo
- MVP is progressive
- prophylactic antibiotics to prevent bacterial endocarditis is warranted

Autosomal Recessive

- Friedreich Ataxia
- Gaucher disease
- Glycogen storage disease
- Hemochromatosis
- Homocystinuria
- Pseudoxanthoma elasticum
- Refsum disease
- Tay-Sachs disease

X - Linked Recessive

- Duchenne and Becker Muscular Dystrophies
- Fabry Disease
- Color blindness

Multifactorial Causation

- disease or trait is due to environmental influences and polygenic predisposition
- Isolated birth defects: congenital heart defects, cleft lip and palate, neural tube defects, pyloric stenosis
- diseases that may have : DM, asthma, hypertension, coronary artery disease, atherosclerosis